TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
C1-A0404P		
International application No	International filing date (day/month/year)	Priority date (day/month/year)
PCT/JP2004/005152	09.04.2004	

International Patent Classification (IPC) or national classification and IPC

C12N15/09 C07K16/28 C07K16/46 A61P35/00 A61P37/02 A61P43/00 A61K39/395

Applicant

CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of _____ sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions)

☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.

b. ☒ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

1 Disc , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒ Box No. I Basis of the report

☐ Box No. II Priority

☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

☐ Box No. IV Lack of unity of invention

☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

☒ Box No. VI Certain documents cited

☐ Box No. VII Certain defects in the international application

☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No
PCT/JP2004/005152

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following _____ which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No
PCT/JP2004/005152

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-14	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-14	NO
Industrial applicability (IA)	Claims	1-14	YES
	Claims		NO

2 Citations and explanations (Rule 70.7)

Document 1: Hudson P. J. et al., High avidity scFv multimers; diabodies and triabodies, J Immunol Methods, 1999, Vol. 231, pages 177-189

Document 2: Kortt A. A. et al., Dimeric and trimeric antibodies: high avidity scFvs for cancer targeting, Biomol Eng, 2001, Vol. 18, pages 95-108

Document 3: Xiong D. et al., Efficient inhibition of human B-cell lymphoma xenografts with an anti-CD20 x anti-CD3 bispecific diabody, Cancer Lett, 2002, Vol. 177, pages 29-39

Document 4: Matsuoka S. et al., A novel type of cell death of lymphocytes induced by a monoclonal antibody without participation of complement, J Exp Med, 1995, Vol. 181, pages 2007-2015

Document 5: Fayen J. et al., Negative singalling by anti-HLA class I antibodies is dependent upon two triggering events, Int Immunol, 1998, Vol. 10, pages 1347-1358

Document 6: Woodle E. S. et al., Anti-human class I MHC antibodies induce apoptosis by a pathway that is distinct from the Fas antigen-mediated pathway, J Immunol, 1997, Vol. 158, pages 2156-2164

Document 7: Tahtis K. et al., Biodistribution properties of (111)indium-labeled C-functionalized trans-cyclohexyl diethylenetriaminepentaacetic acid humanized 3S193 diabody and F(ab')(2) constructs in a breast carcinoma xenograft model, Clin Cancer Res, 2001, Vol. 7, pages 1061-1072

Document 8: Rossi E. A. et al., Development of new multivalent-bispecific agents for pretargeting tumor localization and therapy, Clin Cancer Res, 2003, Vol. 9, pages 3886S-3896S

The subject matters of claims 1-7 do not appear to involve an inventive step in view of documents 1-8 cited in the ISR.

Documents 1-3 respectively are considered to disclose that efficient crosslinking of two antigens can be performed by the use of a diabody. Documents 4-6 respectively are also considered to disclose that various anti HLA antigens are able to induce apoptosis in various cells (for example, T cells and B cells) by crosslinking with a target cell surface antigen. Furthermore, that a diabody having a given CDR can be produced by using a variable region of a humanized antigen having the given CDR introduced therein had been well known prior to the filing date of the present application, as described in documents 7 and 8.

So, in the inventions described in documents 4-6, a person skilled in the art could have easily conceived of attempting to employ the diabody described in documents 1-3 to achieve efficient crosslinking with an antigen on the surface of a target cell for the purpose of efficiently inducing

apoptosis.

In so doing, a person skilled in the art could have, as a matter of course, produced and employed a diabody having a CDR derived from an anti-HLA antigen, since the inventions described in documents 4-6 induce apoptosis by the use of an anti-HLA antigen. In addition, as the anti-HLA antigen from which the said CDR is derived, a person skilled in the art could have accordingly employed an appropriate anti-HLA antigen selected from a group of anti-HLA antigens acquired by a given well-known technique.

Therefore, the subject matters of claims 1-7 of the present application incorporating such a constitution are not considered to assure an especially superior effect in cytotoxic activity or antitumor effect to the inventions described in documents 1-8.

The subject matters of claims 8-14 do not appear to involve an inventive step in view of documents 1-8 cited.

Employing the aforesaid diabody for an apoptosis-inducing agent, antitumor medicine, and autoimmune disease therapeutic agent is a matter that a person skilled in the art could have easily conceived as required.

In addition, incorporating such a constitution into the subject matters of claims 1-7 of the present application is not considered to assure an especially superior effect in cytotoxic activity or antitumor effect to the inventions described in documents 1-8 either.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/005152

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 04/033499 A1 [EX]	22.04.2004	10.10.2003	11.10.2002

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/005152

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1 With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☒ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed

☒ filed together with the international application in computer readable form

☐ furnished subsequently to this Authority for the purposes of search and/or examination

☐ received by this Authority as an amendment* on _____

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3 Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*